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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/978,632	11/25/1997	ELAZAR RABBANI	ENZ-53(C)	4638

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ENZO BIOCHEM, INC.
527 MADISON AVENUE (9TH FLOOR)
NEW YORK, NY 10022

EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	
MAIL DATE	DELIVERY MODE
01/20/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	08/978,632	RABBANI ET AL.	
	Examiner	Art Unit	
	KIMBERLY CHONG	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 September 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *246-252,255,264,265,271,273,274 and 276-279* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *246-252,255,264,265,271,273,274 and 276-279* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 09/10/2010 to the Final Rejection mailed 03/10/2010 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 03/10/2010 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Applicant's amendments to the claims filed 09/10/2010 have been entered into the application. With entry of the amendment, claims 246-252, 255, 264, 265, 271, 273, 274 and 276-279 are pending and examined herein.

New Claim Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 273 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 273 is drawn to a construct comprising at lest 3 strands comprising a non-nucleic acid entity and wherein the first segment of the second strand is complementary to this entity. Applicant has not pointed to any specific location in the instant specification for this claim amendment. The specification does not appear to disclose such a construct.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

Claim 273 us rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim in drawn to a modified nucleic acid construct at least three strands wherein the first strand is a template strand, which as understood from the specification is used for the synthesis of a product having biological activity. The second strand has at least one terminus that comprises a polynucleotide tail. It is unclear how the second strand can comprise a terminus, which would be the end of a strand but also at this end comprise a polynucleotide tail. This description is vague and it is unclear if the terminus as described would be the end of the polynucleotide tail. The claims also recites the second strand has two segments, one which is complementary to the first strand and a second which is not and is complementary to the first strand but comprises a

polynucleotide tail. The claims further recite the polynucleotide tail of the second strand is complementary to a third strand which comprises the non-nucleic acid moiety.

The claims are written are very vague and ambiguous and do not particularly point out the claimed construct. It is not clear if the construct is linear or circular, comprises nicks due to the second strand having two segments and a "terminus".

As such the claim has not been further examined on the merits.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 271 is rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Myers (EP 0 273 085; of record).

The instant specification teaches that cell targeting entities include proteins that have affinity for cell surfaces.

In one embodiment, Claim 271 is drawn to a chemically modified double stranded nucleic acid construct comprising a modified nucleotide that comprises a polymer. A modified nucleotide is reasonably considered to embrace any nucleotide that has been changed or altered from its natural form, as occurs when a non-nucleic acid molecule is attached to a nucleotide. Logically, the attachment of a non-nucleic acid entity to a nucleotide, such as a protein, represents a modification to that nucleotide.

Therefore, a nucleotide that is linked to a protein is a modified nucleotide that contains a non-nucleic acid moiety.

Myers taught a modified double stranded nucleic acid construct that expresses a protein and therefore messenger RNA (i.e., sense RNA) in a cell. See Fig. 2, Detailed Description of the Invention, Examples 1-4, and Claims 1-13. The construct comprises double stranded DNA conjugated to at least one molecule of epidermal growth factor (EGF). See column 3, beginning at line 55; column 6, lines 19-20; and Fig. 2. The EGF molecule, when covalently attached to a double stranded nucleic acid, is shown to facilitate entry of the nucleic acid into the cell (Exs. 3-5).

The method used to couple EGF to the double stranded DNA results in attachment of EGR to a 5'-phosphate, thereby producing a modified nucleotide (col. 3, line 55). Accordingly, in view of the efficiency and randomness of the chemical reaction, and noting there are only two 5'-phosphates in a linear dsDNA molecule, it is reasonable to presume that the method used by Myers to produce the EGF-dsDNA conjugate results in some dsDNA molecules having one EGF molecule in solely one strand of the dsDNA, as shown in Fig. 2 and as suggested by characterization of the conjugates at column 6, lines 19-20. Thus, the presence of EGF in solely one strand of the nucleic acid is an outcome that is inherent to the method used to make the constructs. Notwithstanding this fact, one of skill would reasonably have predicted that the constructs disclosed by Myers would have the same properties and would function in substantially the same manner regardless of whether the constructs contained one or two molecules of EGF molecules.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g)

Claims 246-252, 255, 264, 265, 274 and 276-279 are rejected under 35 U.S.C. 103(a) as being anticipated by Craig et al. (US Patent 5,766,902), Wagner et al. (PNAS 1992 of record) and Perales et al. (Eur. J. Biochem Vol. 226: 255-266).

The claims are drawn to a chemically modified nucleic acid construct comprising a fusogenic peptide, a ligand to a cell receptor and a non-nucleic acid entity that confers nuclear localization.

Craig et al. taught methods for enhancing the targeted delivery of nucleic acid molecules to cells by coupling the nucleic acid to a ligand having affinity for a cell surface molecule or receptor. The ligand facilitates uptake of the nucleic acid by receptor mediated endocytosis (cols. 2-6). The nucleic acid molecule preferably comprises at least one transcription unit encoding a protein or RNA molecule such as an antisense oligonucleotide or ribozyme (col. 3, lines 59-62; col. 4, lines 24-28). The nucleic acid molecule may be plasmid DNA or a recombinant viral genome, such as any adenoviral or retroviral vector (col. 12, lines 1-25). Thus, the types of nucleic acids contemplated for use with the invention include single and double stranded, linear and circular, DNA and RNA molecules. The ligand may be any molecule, small or large, capable of binding to a cell and/or facilitating delivery into the cell (col. 4, lines 29-45), including proteins, carbohydrates, and metal ions. Specifically recommended are antibodies, growth factors, and fusogenic peptides (col. 4 and 8). The ligand may be chemically conjugated by covalent bonded to the nucleic acid (col. 8, lines 14-15). Covalent conjugation would necessarily result in modification of the sugar, phosphate, or nucleobase portion of one or more nucleotides of the nucleic acid. Therefore, the construct would comprise a modified nucleotide and nucleotide analog, since, according to Applicant, modified nucleotides are nucleotide analogs. Craig et al. disclosed that a DNA construct may also be associated with a fusogenic protein (see column 8 of Craig

et al.). Specifically, Craig et al. stated that "Delivery of the foreign DNA into the target cell may also be achieved via the DNA construct's association with an endosomal disruption agent, such as the influenza hemagglutinin fusogenic peptide."

The construct taught by Craig et al. does not specifically teach a construct comprising a fusogenic peptide and a ligand to a cell receptor and an entity that confers nuclear localization.

Wagner et al. teach the use of ligand mediated constructs to deliver DNA to cells and state that delivery from endosomes is a limiting step that can be solved by the additional use of a fusogenic peptide such as the influenza hemagglutinin fusogenic peptide.

Perales et al. discuss the concept of ligand mediated delivery of DNA and outlines the design elements that are useful. Perales et al. teach the DNA ligand needs to be efficiently transported to the nucleus and this active process that requires the use of nuclear localization elements and lists a few proteins for this purpose (see page 262).

It would have been obvious to one of ordinary skill in the art to incorporate a fusogenic peptide and a nuclear localization entity into the construct taught by Craig et al.

One would have been motivated given Wagner et al. teach transfer of a DNA ligand complex from the endosome is an essential step which can be solved by the use of a fusogenic peptide and Perales et all. teach the use of nuclear localization elements are necessary for active localization of the complex in the nucleus. One of ordinary skill

in the art would have expected to be able to incorporate these elements into the construct as the steps are routine and taught in the prior art.

Response to Arguments

Double Patenting

Claims 246-252, 255, 264, 265, 271, 273, 274 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 245-248, 251, 253, 261-265, 306, and 307 of copending Application No. 08/978,633. New claims 276-279 would have been previously rejected in the previous Office action to the rejection of record applies to these newly added claims.

In the reply filed 09/10/2010, Applicant states the provisional rejection will be addressed once there is an indication of allowable subject matter. The reply does not present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references (37 CFR 1.111(b)).

The Examiner notes allowable subject matter has not yet been identified. Accordingly, the provisional rejection is maintained for the reasons of record, reiterated above.

Claim Rejections - 35 USC § 102

The rejection of claims 246-252, 255, 264, 265, and 271-275 under 35 U.S.C. 102(e) as being anticipated by Craig et al. (US Patent 5,766,902) is withdrawn in view of the claim amendments and new rejection above.

Claim Rejections - 35 USC § 103

The rejection of claims 250, 251, 271, 272, 273, and 275 under 35 U.S.C. 103(a) as being unpatentable over Hirsch et al. (1993) *Transplantation Proceedings* 25:138-139 as applied to claims 246-249, 252, 255, 264, and 265 above, and further in view of Keating et al. (US Patent 6,503,755); Bos et al. (1992) *Hybridoma* 11:41-51; and Smith-Ravin et al. (1989) *Int. J. Radiat. Biol.* 56:951-961 is withdrawn in view of the claim amendments and new rejection above.

Prior art made of record but not currently relied on

The following prior art is made of record and is not relied upon, but is considered pertinent to applicant's disclosure.

Ramsay-Shaw et al. (US Patent 5,683,869) taught boranophosphate modified oligonucleotides for incorporation into DNA Vectors. The boranophosphate linkages are said to confer nuclease resistance. The modified vectors can be used for a variety of purposes including directed gene transfer and expression (col. 16, lines 15-45).

Putney et al. (1981) *Proc. Natl. Acad. Sci.* 78:7350-7354 taught methods for making and using phosphorothioate modified plasmid DNA.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful please contact Acting SPE for 1635 Heather Calamita at 571-272-2876. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Kimberly Chong/
Primary Examiner
Art Unit 1635